DETAILED ACTION

Formal Matters and Claim status

This action is in response to papers filed 2/8/2010.

The claims 2-5, 7-11, 14-26, 28-35, 37-45, 47-51, 54-59, 61-96 are canceled.

Claims 97-102 have been added by amendment.

Claims 1, 6, 12-13, 27, 36, 46, 52-53, 60, and 97-102 are pending.

The objection to claims 52 and 53 have been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112-New Grounds

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 6, 12-13, 27, 36, 46, 52-53, 60, and 97-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 27, 36, 46, and 60 have been amended to recite, "On the accellular DNA" and "on a control DNA." It is unclear if the claim requires markers that are a part of the accellular or control DNA backbone, DNA that can hybridize to the control or accellular DNA, or markers that are on the accellular or control DNA through interaction with a protein or some type of covalent modification. Claims 12-13, 52-53 and 97-102 are rejected as they depend from the independent claims.

The rejected claims all recite, "Wherein the DNA markers are further amplified before the determination of loss of heterozygosity of the accellular DNA, wherein the

DNA markers that have lost heterozygosity and the DNA markers that have retained heterozygosity are both amplified." Thus the claims appear to require amplification of DNA markers that have a loss of heterozygosity and thus are no longer present on the DNA. It is unclear how one would amplify nucleic acid sequence that have been lost.

Claim Rejections - 35 USC § 103-Maintained

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 6, 12, 13, 27, 97, 98, and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504, issued Dec 5, 2000).

This rejection was previously presented but has been modified to reflect the claim amendments and improve clarity.

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells (control) were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma, serum, or blood as a sample (1, 6, 12, 13, 26, 27, 74).

However, Gocke et al teaches methods of using of extracellular DNA found serum (2, 7) or plasma (claims 3,8,) for the detection of cancer (see title, abstract). Gocke teaches peripheral blood (claims 81, 82,); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-55). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of blood, plasma, or serum allows rapid and timely extraction and sensitive detection of extra cellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting the presence of markers D12S1657, D12S393, D12S1706, and D12S346 by amplification of accellular DNA and comparing to a control sample by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. It would have been obvious to one of ordinary skill in the art to use DNA normal tissue as a control as Soegnas teaches. The ordinary artisan would further be motivated because, Gocke teaches use of plasma or serum allows rapid and timely extraction and sensitive detection of extracellular tumor associated or extracellular mutated oncogenic DNA. Thus as Gocke teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Gocke would have resulted

in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in accellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma.

Response to Arguments

The response reproduces portions of column 3 of Gocke, in which Gocke addresses the state of the prior art which did not recognize the novel findings of Gocke as to the usefulness of extracellular DNA.

The response continues, “Gocke provided a method of "preferential" amplification of the mutant DNA over the wildtype but not mutant extracellular DNA by selective digestion of the wildtype but not mutant DNA before and/or during and optionally after DNA amplification so that the mutant DNA is selectively amplified. ("Preferably, digestion of the extracted extracellular nucleic acid with an enzyme, ... specifically cleaves wildtype but not mutant DNA in the portion of the sequence between the positions of the oligonucleotide primers used to amplify the DNA. Thus wildtype DNA in the sample cannot be amplified after restriction enzyme digestion, whereas mutant DNA can be amplified, and is preferentially amplified using the method of the invention.., the amplification reaction is performed in the presence of a thermoresistant or thermostable restriction endonuclease, which endonuclease specifically cleaves wildtype (but not mutant) forms of extracellular tumor derived or tumor-associated nucleic acid species and therefore inhibits amplification of said species in the amplification..." (Lines 48-63, column 4.)” Thus the response has provided one embodiment of Gocke in which mutant DNA is preferentially amplified over mutant. However, Gocke teaches, “n a first

aspect, the invention provides a method for detecting extracellular tumor-derived or tumor-associated nucleic acid in a plasma or serum fraction of a blood sample, for diagnosis, detection, monitoring, evaluation or treatment of a neoplastic or proliferative disease in an animal or a human. The method provided by the invention comprises the steps of: first, purifying extracellular nucleic acid from plasma or serum to prepare a homogeneous preparation of extracted nucleic acid; second, specifically amplifying a portion of the extracted nucleic acid to provide an amplified nucleic acid fraction comprising a nucleic acid that is associated with neoplastic or proliferative disease; and third, detecting the amplified nucleic acid fragment that is associated with neoplastic or proliferative disease in the amplified nucleic acid fraction. In preferred embodiments of this aspect of the invention, extracted nucleic acid is amplified using an amplification method selected from the group consisting of polymerase chain reaction, ligase chain reaction, branched DNA signal amplification, boomerang DNA amplification, Q-beta replication, transcription-based amplification, isothermal nucleic acid sequence based amplification, self-sustained sequence replication assay, strand displacement activation, cycling probe technology, and combinations or variations thereof. In another preferred embodiment, the nucleic acid is derived from a nucleic acid encoding an oncogene or other tumor-associated DNA" (column 4).

The response continues by asserting that the amendment to require, "comparing one or more DNA markers of the accellular DNA with that on a control DNA for determination of loss of heterozygosity of the accellular DNA" have over come the instant rejection as the response asserts the teachings of Gocke (column 4, lines 48-63)

teach away from the instant invention. The response specifically asserts, "Gocke teaches an ordinary artisan could amplify the mutant, not the wildtype DNA." These arguments have been thoroughly reviewed but are not considered persuasive as the claims do not require that the control DNA be the wildtype sequence or the control is obtained from an accellular sample. The arguments appear to allege the claims require that accellular DNA is used as a control, however these are limitations that are not present in the claims.

Thus the rejection is maintained.

6. Claims 46 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504, issued Dec 5, 2000) as applied to claims 1, 6, 12, 13, 27, 97, 98, and 99 above, and further in view of Taback et al (Cancer Research (2001) volume 61, pages 5723-5726) and Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751).

The teachings of Soegnas and Gocke are set forth above.

Soegnas and Gocke do not teach providing samples with stage III or Stage IV melanoma.

However, Taback teaches loss of heterozygosity of microsatelite markers in stage III and stage IV melanoma is associated with a decreased probability of survival (figure 1). Taback teaches, “The findings of additional LOH in more advanced tumors (i.e., highly invasive primary lesions and advanced metastasis) suggests that these additional events, not always present in early stages of primary tumors, may be

associated with, or representative of, more aggressive tumors that may be of prognostic value" (page 5723, 2nd column, 1st paragraph). Taback further teaches that once melanoma has metastasized, overall prognosis is generally poor (page 5725, 1st column, 1st full paragraph).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31
Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the

Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze stage III or stage IV melanoma as taught by Taback and Chapman in the method of Soegnas and Gocke. The artisan would be use stage III or stage IV melanoma samples in the method of Soengas as there are only four stages of melanoma known and thus a limited number of possibilities. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with LOH of stage III or stage IV melanoma have a poor prognostic outcome and further because Chapman teaches subjects with Stage IV have poor prognosis and survival, while Soegnas and Gocke teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 relative to a control is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

Response to Arguments

The response reiterates the arguments previously presented with respect to Soegnas and Gocke. These arguments have been previously addressed.

7. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al (US Patent 6156504, issued Dec 5, 2000), Taback et al (Cancer Research (2001)

volume 61, pages 5723-5726) and Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751) as applied to claim 46 above, and further in view of Yu et al (Cancer (1999) volume 86, pages 612-627).

The teachings of Soengas, Gocke, Taback, and Chapman are set forth above.

Soengas, Gocke, Taback, and Chapman do not teach melanoma being regional lymph node metastasis (RLM) or in transit metastasis (ITM).

However, Yu teaches early detection of AJCC stage III metastasis's to regional lymph nodes (RLM) (page 625, 2nd column 1st paragraph). Yu further teaches melanoma metastasis in transit were known (page 620, 1st column, 1st full paragraph).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze IRM or ITM melanoma as taught by Yu in the method of Soengas, Gocke, Taback, and Chapman. The artisan would be use IRM or ITM melanoma samples in the method of Soengas, Gocke, Taback, and Chapman as there are known forms of melanoma mestasis. The artisan would have a reasonable expectation of success of determining a low probability of survival of patients with metastatic melanoma including IRM and ITM because Soengas teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 is associated with decreased apoptosis in response to chemotherapy and thus poor outcome.

Response to Arguments

The response asserts that claims have been amended to depend from claim 46, which was not previously rejected. This argument has been thoroughly reviewed but is not considered persuasive as claim 46 has been amended in the instant response and

is rejected. Further the limitations were addressed in the previous action as claim 45, which was an obvious typographical error by the examiner as claim 45 had been previously canceled. Thus the rejection is maintained.

8. Claims 1, 6, 12, 13, and 27, are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571).

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines12-14). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of accellular DNA from plasma, serum, or blood as a sample (1, 6, 12, 13, and 27).

However, Fujiwara teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph). Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, “The study also demonstrated that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, “This study illustrates the clinical se or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more

suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. " Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use. Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs (38, 39). These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression." Page (1570, 1st column)

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Fujiwara, because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Fujiwara teaches, "The most significant advantage of this approach in assessing plasma

compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques." Thus as Fujiwara teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Fujiwara would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in accellular DNA from blood, serum, or plasma and from this detection allow the detection of melanoma.

Response to Arguments

The response further asserts the teachings of Fujiwara suggest that LOH of DNA markers are not necessarily identical or consistent in tumor cells and accellular DNA. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require comparison to a tumor sample and thus the arguments are beyond the scope of the claimed invention. Further Fujiwara teaches, "We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs (38, 39). These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression." (page 1570, 1st column). Fujiwara further teaches, "the assay is very specific in that none of the normal samples tested showed LOH at any loci" (page 1570, 2nd column, 1st full paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH

in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, "This study illustrates the clinical se or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demon- strafes that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage It to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. "Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use.

Thus for the reasons of record the rejection is maintained.

9. Claims 36, 60, 100 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571) as applied to claim 1, 6, 12, 13, 26, 27, 74, above, and further in view of Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751), Healy (oncogene (1998)

volume 16, pages 2213-2218) and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

The claim 36 is drawn to loss of heterozygosity being indicative of poor efficacy of biochemotherapy. The specification does not present a definition of "efficacy" or "poor efficacy." Further the specification nor claims set forth what the efficacy is relative to. Thus poor efficacy is being given the broadest reasonable interpretation as survival after treatment.

The claim 60 is drawn to loss of heterozygosity being indicative of low probability of responsiveness to biochemotherapy. The specification does not present a definition of "low probability of responsiveness." Thus of low probability of responsiveness is being given the broadest reasonable interpretation as survival after treatment.

The teachings of Fujiwara and Soegnas are set forth above.

Soengas and Fujiwara do not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy. Soengas and Fujiwara do not teach melanoma biochemotherapy comprising dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median

survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman teaches, "Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.31 Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm" (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus

poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Healy teaches, "Some (but not all) studies on DNA ploidy in melanoma have suggested that individuals with tumours exhibiting aneuploidy have a poorer out-come" (page 2213, 2nd column, last paragraph). Healy further teaches, "metastatic melanoma is a late stage of disease, and nearly all patients with metastases will eventually die from their melanoma" (page 2213, 2nd column, last paragraph). Healy further teaches, "However, based on the FAL scores, the results suggest that the overall level of genomic instability (as well as losses of 6q and 10q) may determine the clinical behavior of the melanoma and the ultimate clinical survival. This association of higher FAL scores with a poorer clinical, outcome, independent of the depth of invasion, suggests that this variable might allow the identification both of individuals with thin melanomas who will eventually die from their tumour and of subjects with paradoxically thick melanomas in whom the melanoma will not metastasize." (page 2215, 2nd column, last paragraph).

Further O'Day et al teaches "5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals" (see abstract). O'Day teaches pretreatment evaluation (page 2753, 2nd column). O'Day further teaches, "the concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-

stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.29, 30 Routine post treatment G-CSF was implemented because of the high incidence of grade myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 27531st column, 2nd full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the teachings of Soengas and Fujiwara with a reasonable expectation of success. Chapman and Healy teach that subjects with stage IV melanomas and metastasis had poor longer term prognosis and thus poor response to biochemotherapy. Chapman teaches only 5% to 20% of subjects with stage IV melanoma responded to biochemotherapy, while Healy teaches genomic instability plays a large role in clinical outcome. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn

results in increased chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to treatment a chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents (dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen). It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas and Fujiwara suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

Response to Arguments

The response reiterates the arguments previously presented with respect to Soegnas and Fujiwara. These arguments have been previously addressed.

Conclusions

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Primary Examiner, Art Unit 1634